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CHEMICAL ABSTRACTS, vol. 83, no. 13, September 29, 1975, Columbus, Ohio, USA; J. SOLODAR, "Asymmetric hydrogenation of ketones", page 488, column 2, abstract no. 113607k
CHEMICAL ABSTRACTS, vol. 94, no. 15, April 13, 1981, Columbus, Ohio, USA; A. TAI, "Asymmetrically modified nickel catalyst and its use for the preparation of optically active 3-hydroxy acids", page 631, column 1, abtract no. 120759s

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Description

This invention relates to a process for preparing an optically active alcohol useful as intermediate for synthesizing pharmaceuticals, liquid crystal material, and the like by asymmetric hydrogenation of a β-keto acid derivative in the presence of a ruthenium-optically active phosphine complex as a catalyst.

Known techniques for asymmetrically synthesizing optically active alcohols include a process comprising asymmetric hydrogenation using baker's yeast and a process comprising asymmetric hydrogenation using a specific catalyst.

In particular, with respect to asymmetric hydrogenation of ℓ-keto acid derivatives to obtain optically active alcohols, it has been reported that the asymmetric hydrogenation can be carried out by using a rhodium-optically active phosphine complex as a catalyst. For example, J. Solodar reports in Chemtech., 421-423 (1975) that asymmetric hydrogenation of methyl acetoacetate gives methyl 3-hydroxybutyrate in an optical yield of 71%ee.

Further, asymmetric hydrogenation using a tartaric acid-modified nickel catalyst has been proposed. According to this technique, asymmetric hydrogenation of methyl acetoacetate gives methyl 3-hydroxybutyrate in an optical yield of 85%ee as disclosed in Tai, Yukagaku, 822-831 (1980).

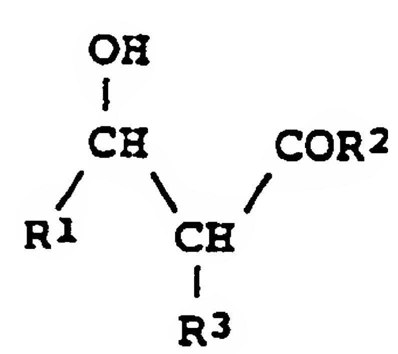
Although the process using baker's yeast produces an alcohol having relatively high optical purity, the resulting optically active alcohol is limited in absolute configuration, and synthesis of an enantiomer is difficult.

The process utilizing asymmetric hydrogenation of β-keto acid derivative in the presence of a rhodium-optically active phosphine complex does not produce an alcohol having sufficient optical purity. Besides, metallic rhodium to be used in the catalyst is expensive due to limitations in place and quantity of production. When used as a catalyst component, it forms a large proportion in cost of the catalyst, ultimately resulting in increase in cost of the final commercial products.

The process using a tartaric acid-modified nickel catalyst involves the disadvantages of difficulty in preparing the catalyst and insufficient optical yield.

As a result of extensive investigations with the purpose of meeting the above-described problems, the inventors have found that an optically active alcohol having high optical purity can be obtained by asymmetric hydrogenation of a β-keto acid derivative in the presence of a relatively cheap ruthenium-optically active phosphine complex as a catalyst. The present invention has been completed based on this finding.

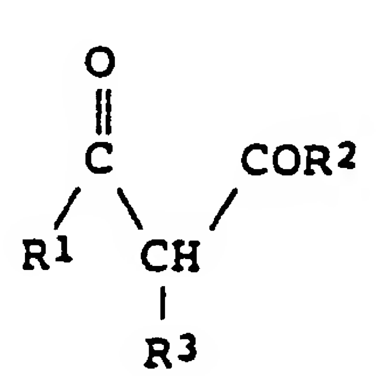
The present invention relates to a process for preparing an optically active alcohol represented by formula (I):



(I)

wherein R^1 represents a substituted or unsubstituted lower alkyl group, a trifluoromethyl group or an aryl group; R^2 represents OR^4, wherein R^4 represents an alkyl group having from 1 to 8 carbon atoms, SR^5, wherein R^5 represents a lower alkyl group or a phenyl group, or NR^6R^7, wherein R^6 and R^7, which may be the same or different, each represents a hydrogen atom, a lower alkyl group or a benzyl group; and R^3 represents a hydrogen atom, a halogen atom, a lower alkyl group, a lower alkoxycarbonyl group or a lower alkoxycarbonyl-lower alkyl group; or R^1 and R^3 are connected to each other to form a methylene chain, forming a 4- to 6-membered ring together with the carbon atoms therebetween,

which comprises asymmetrically hydrogenating a β-keto acid derivative represented by formula (II):



(II)

wherein R^1, R^2, and R^3 are as defined above,
in the presence of a ruthenium-optically active phosphine complex as a catalyst.

The "lower" alkyl or alkoxy groups have 1 to 7, preferably 1 to 4 carbon atoms.

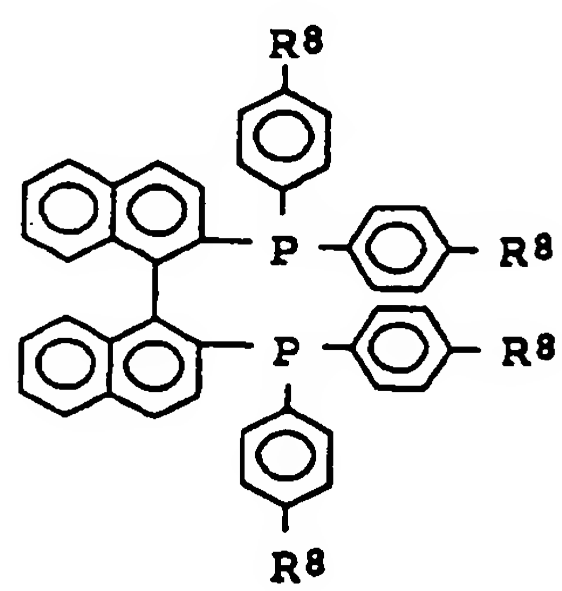
In formulae (I) and (II), substituents for the lower alkyl group as represented by R^1 include a halogen atom, a hydroxyl group, an amino group, a lower alkyl-substituted amino group, a benzyloxy group, and an aryl group.

The β-keto acid derivative represented by formula (II) which can be used in the present invention as a starting compound specifically includes methyl acetoacetate, ethyl acetoacetate, isopropyl acetoacetate, n-butyl acetoacetate, t-butyl acetoacetate, n-pentyl acetoacetate, n-hexyl acetoacetate, n-heptyl acetoacetate, n-octyl acetoacetate, methyl 4-chloroacetoacetate, ethyl 4-chloroacetoacetate, methyl 4-fluoroacetoacetate, methyl 3-oxopentanoate, methyl 3-oxohexanoate, methyl 3-oxoheptanoate, ethyl 3-oxooctanoate, ethyl 3-oxononanoate, ethyl 3-oxodecanoate, ethyl 3-oxoundecanoate, ethyl 3-oxo-3-phenylpropanoate, ethyl 3-oxo-3-p-methoxyphenylpropanoate, ethyl 4-phenyl-3-oxobutanoate, methyl 5-phenyl-3-oxopentanoate, ethyl 3-trifluoromethyl-3-oxopropanoate, ethyl 4-hydroxy-3-oxobutanoate, methyl 4-benzyloxy-3-oxobutanoate, ethyl 4-benzyloxy-3-oxobutanoate, methyl 4-amino-3-oxobutanoate, ethyl 4-methylamino-3-oxobutanoate, methyl 4-dimethylamino-3-oxobutanoate, ethyl 4-dimethylamino-3-oxobutanoate, ethyl 2-methylacetoacetate, ethyl 2-chloroacetoacetate, diethyl 2-acetylsuccinate, diethyl 2-acetylglutalate, 2-carboethoxy-cyclopentanone, 2-carboethoxy-cyclohexanone, dimethyl acetylmalonate, 3-oxobutanoic dimethylamide, 3-oxobutanoic benzylamide, thiomethyl acetoacetate, thioethyl acetoacetate and thiophenyl acetoacetate.

The ruthenium-optically active phosphine complex to be used as a catalyst include those represented by the following formulae (III) and (V):

$$Ru_xH_yCl_z(R^8\text{-}BINAP)_2(S)_p \qquad (III)$$

wherein R^8-BINAP represents a tertiary phosphine represented by formula (IV):



(IV)

wherein R^8 represents a hydrogen atom, a methyl group or a t-butyl group; S represents a tertiary amine; when y represents 0, then $\underline{x}$ represents 2, $\underline{z}$ represents 4, and $\underline{p}$ represents 1; and when $\underline{y}$ represents 1, then $\underline{x}$ represents 1, $\underline{z}$ represents 1; and $\underline{p}$ represents 0.

$$[RuH_\ell(R^8\text{-}BINAP)_v]Y_w \qquad (V)$$

wherein R^8-BINAP is as defined above; Y represents ClO_4, BF_4 or PF_6; when $\underline{\ell}$ represents 0, then $\underline{v}$ represents 1, and $\underline{w}$ represents 2; and when $\underline{\ell}$ represents 1, then $\underline{v}$ represents 2 and $\underline{w}$ represents 1.

In formulae (III) and (V), "BINAP" represents a 2,2-bis(diphenylphosphino)-1,1'-binaphthyl moiety (hereinafter the same).

The compound of formula (III) can be obtained by the process disclosed in T. Ikariya et al., J. Chem. Soc., Chem. Commun., 922-924 (1985) and Japanese Patent Application (OPI) No. 63690/86 (the term "OPI" as used herein means "unexamined published Japanese patent application"). More specifically, the complex of formula (III) wherein y is 0 can be prepared by reacting 1 mol of $[RuCl_2(COD)]_n$ (wherein COD represents cycloocta-1,5-diene, hereinafter the same), which is obtainable by reacting ruthenium chloride and COD in an ethanol solution, and 1.2 mols of a 2,2'-bis(di-p-R^8-phenyl-phosphino)-1,1'-binaphthyl (R^8-BINAP) in a solvent, e.g., toluene or ethanol, in the presence of 4 mols of a tertiary amine, e.g., triethylamine. The complex of formula (III) wherein $\underline{y}$ is 1 can be obtained by reacting 1 mol of $[RuCl_2(COD)]_n$, 2.25 mols of R^8-BINAP, and 4.5 mols of a tertiary amine.

The complex of formula (V) wherein $\underline{\ell}$ is 0, $\underline{v}$ is 1 and $\underline{w}$ is 2 can be prepared by reacting $Ru_2Cl_4(R^8\text{-}BINAP)_2(NEt_3)$ (wherein Et represents an ethyl group, hereinafter the same), which is obtained by the above-described process, with a salt represented by formula (VI):

$$MY \qquad (VI)$$

wherein M represents Na, K, Li, Mg or Ag; and Y is as defined above, in a solvent system comprising water and methylene chloride in the presence of a quaternary ammonium salt or quaternary phosphonium salt represented by formula (VII):

$$R^9R^{10}R^{11}R^{12}AB \qquad (VII)$$

wherein R^9, R^{10}, R^{11}, and R^{12} each represents an alkyl group having from 1 to 16 carbon atoms, a phenyl group or a benzyl group; A represents a nitrogen atom or a phosphorus atom; and B represents a halogen atom, as a phase transfer catalyst. The reaction can be carried out by adding the reactants and the phase transfer catalyst of formula (VII) to a mixed solvent of water and methylene chloride and stirring the system. The amounts of the salt of formula (VI) and the phase transfer catalyst of formula (VII) to be added range from 2 to 10 mols, and preferably 5 mols, and from 1/100 to 1/10 mol, respectively, per mol of ruthenium. The reaction sufficiently proceeds by stirring at a temperature of from 5 to 30°C for a period of from 6 to 18 hours, and usually 12 hours. Examples of the phase transfer catalyst of formula (VII) are described in literature, i.e., W.P. Weber and G.W. Gokel, Sokan Ido Shokubai (Japanese translation), 1st Ed., Kagaku Dojinsha (1978). After completion of the reaction, the reaction mixture is allowed to stand still, followed by liquid separation. After the aqueous layer is removed, the methylene chloride solution is washed with water, and methylene chloride is removed by distillation under reduced pressure to obtain the desired compound.

The complex of formula (V) where ℓ is 1, v is 2 and w is 1 can be prepared by reacting $RuHCl(R^8\text{-BINAP})_2$ obtainable by the process disclosed in Japanese Patent Application (OPI) No. 63690/86 with the salt of formula (VI) in a mixed solvent of water and an organic solvent, e.g., methylene chloride, in the presence of the phase transfer catalyst of formula (VII). The amounts of the salt of formula (VI) and the phase transfer catalyst of formula (VII) range from 2 to 10 mols, and preferably 5 mols, and form 1/100 to 1/10 mol, respectively, per mol of ruthenium. This reaction sufficiently proceeds by stirring at a temperature of from 5 to 30°C for a period of from 6 to 18 hours, and usually 12 hours.

Specific examples of the above-described ruthenium-phosphine complex according to the present invention are shown below.

$Ru_2Cl_4(BINAP)_2(NEt_3)$

$Ru_2Cl_4(T\text{-BINAP})_2(NEt_3)$

[T-BINAP represents 2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl]

$Ru_2Cl_4(T\text{-Bu-BINAP})_2(NEt_3)$

[t-Bu-BINAP represents 2,2'-bis(di-p-t-butylphenylphosphino)-1,1'-binaphthyl]

$RuHCl[BINAP]_2$

$RuHCl[T\text{-BINAP}]_2$

$RuHCl[t\text{-Bu-BINAP}]_2$

$[Ru(BINAP)]\ (ClO_4)_2$

$[Ru(T\text{-BINAP})]\ (ClO_4)_2$

$[Ru(t\text{-Bu-BINAP})]\ (ClO_4)_2$

$[Ru(BINAP)]\ (BF_4)_2$

$[Ru(T\text{-BINAP})]\ (BF_4)_2$

$[Ru(t\text{-Bu-BINAP})]\ (BF_4)_2$

$[Ru(BINAP)]\ (PF_6)_2$

$[Ru(T\text{-BINAP})]\ (PF_6)_2$

$[RuH(BINAP)_2ClO_4$

$[RuH(T\text{-BINAP})_2]ClO_4$

$[RuH(BINAP)_2]BF_4$

$[RuH(T\text{-BINAP})_2]BF_4$

$[RuH(BINAP)_2]PF_6$

$[RuH(T\text{-BINAP})_2]PF_6$

In carrying out the present invention, a β-keto acid derivative of formula (II) is dissolved in an amphiprotic solvent, e.g., methanol, ethanol or methyl cellosolve, or a mixed solvent of such an amphiprotic solvent with another solvent such as tetrahydrofuran, toluene, benzene or methylene chloride. The solution is charged in an autoclave, and from 1/100 to 1/50,000 mol of a ruthenium-optically active phosphine complex is added thereto per mol of the β-keto acid derivative. The hydrogenation reaction is effected under stirring at a temperature of from 5 to 50°C, and preferably from 25 to 35°C, at a hydrogen pressure of from 5 to 100 kg/cm² for a period of from 1 to 48 hours. After completion of the reaction, the solvent is removed by distillation, and the residue is distilled under reduced pressure or subjected to silica gel column chromatography to thereby isolate the desired optically active alcohol of formula (I) in a substantially quantitative yield.

The present invention will now be illustrated in greater detail with reference to Reference Examples and

Examples, but the invention is not limited thereto. In these examples, analytical instruments and conditions used for various analyses are as follows.

1) Gas Chromatography (GC):

SHIMADZU GC-9A manufactured by Shimadzu Corporation

Column:	PEG-20M Silica Capillary, 0.25 mm in diameter and 25 m in length, manufactured by Gasukuro Kogyo Inc.
Measurement Temperature:	100-250°C and increasing at a rate of 3°C/min.

2) High Performance Liquid Chromatography (HPLC):

Hitachi Liquid Chromatography-655A-11 manufactured by Hitachi, Ltd.

Column:	Chemcopack Nucleosil 100-3, 4.6 mm in diameter and 300 mm in length, manufactured by Chemco Co.
Developing Solvent:	Hexane:diethyl ether=7:3; flow rate: 1 ml/min
Detector:	UV Detector 655A (UV-254), manufactured by Hitachi, Ltd.

3) Optical Rotation:

Polarimeter DIP-4, manufactured by Nippon Bunko Kogyo K.K.

4) 31P NMR Spectrum:

JNM-GX400 (161 MHz) manufactured by JEOL Ltd.
Chemical shift was determined by using 85% phosphoric acid as an external standard.

REFERENCE EXAMPLE 1

Synthesis of $Ru_2Cl_4[(+)\text{-BINAP}]_2(NEt_3)$ (di[2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]tetrachloro-diruthenium triethylamine):

To 100 ml of toluene were added 1 g (3.56 mmol) of $[RuCl_2(COD)]_n$, 2.66 g (4.27 mmol) of (+)-BINAP, and 1.5 g of triethylamine in a nitrogen atmosphere, and the mixture was heat-refluxed for 10 hours. The solvent was removed from the reaction mixture by distillation under reduced pressure, and the residual solid was dissolved in methylene chloride, followed by filtration through Celite filter aid. The filtrate was concentrated to dryness to obtain 3.7 g of the entitled compound as a deep brown solid.

Elemental Analysis for $C_{94}H_{79}Cl_4NP_4Ru_2$:

Calcd. (%):	Ru 11.96; C 66.85; H 4.71; P 7.33
Found (%):	Ru 11.68; C 67.62; H 4.97; P 6.94
^{31}P NMR ($CDCl_3$) δ ppm:	51.06 (s), 51.98 (s), 53.87 (s), and 54.83 (s)

REFERENCE EXAMPLE 2

Synthesis of $[Ru((-)\text{-T-BINAP})](ClO_4)_2$ ([2,2'-bis(di-p-tolylphosphino)-1,1'-binaphthyl]ruthenium perchlorate):

In a 250 ml-volume Schlenk's tube was charged 0.54 g (0.3 mmol) of $Ru_2Cl_4[(-)\text{-T-BINAP}]_2(NEt_3)$. After thorough displacement of the atmosphere with nitrogen gas, 60 ml of methylene chloride was added thereto, and then a solution of 0.73 g (6.0 mmols) of sodium perchlorate in 60 ml of water and a solution of 16 mg (0.06 mmol) of triethylbenzylammonium bromide in 3 ml of water were added to the mixture. The mixture was stirred at room temperature for 12 hours. After completion of the reaction, the reaction mixture was allowed to stand, and the aqueous layer was removed. The methylene chloride was removed from the organic layer by distillation under reduced pressure, and the residue was dried under reduced pressure to obtain 0.59 g (yield: 99.6%) of the entitled compound as a deep brown solid.

Elemental Analysis for $C_{48}H_{40}Cl_2O_8P_2Ru$:

Calcd. (%):	Ru 10.32; C 58.90; H 4.12; P 6.33
Found (%):	Ru 10.08; C 58.61; H 4.53; P 5.97

^{31}P NMR ($CDCl_3$) δ ppm: 12.920 (d, J=41.1 Hz) and 61.402 (d, J=41.1 Hz)

EXAMPLE 1

Synthesis of Methyl (3R)-(-)-3-Hydroxybutyrate

In a 200 ml-volume stainless steel-made autoclave whose atmosphere had been replaced with nitrogen were charged 10 ml (93 mmols) of methyl acetoacetate, 50 ml of methanol, and 0.5 ml of water, and 42 mg (0.025 mmol) of $Ru_2Cl_4((+)\text{-BINAP})_2(NEt_3)$ as prepared in Reference Example 1 was added thereto to effect hydrogenation at a temperature of 30°C under a hydrogen pressure of 40 kg/cm² for 20 hours. The solvent was removed by distillation, and the residue was distilled under reduced pressure to obtain 10.8 g (98%) of the entitled compound having a boiling point of 72°C/17 mmHg.

The product was found to have a purity of 99.0% by GC and an optical rotation $[\alpha]_D^{20}$ of -24.17° (neat).

Thirty milligrams of the resulting alcohol was esterified with (+)-α-methoxy-α-trifluoromethylphenylacetyl chloride, and the ester was analyzed by GC and HPLC. The results revealed that the product was a mixture comprising 99.55% of methyl (3R)-(-)-3-hydroxybutyrate and 0.45% of methyl (3S)-(+)-3-hydroxybutyrate. Accordingly, the optical yield of the methyl (3R)-(-)-3-hydroxybutyrate was found to be 99.1%.

EXAMPLES 2 to 17

The same procedure of Example 1 was repeated, except for altering the reaction substrate, catalyst and reaction conditions as shown Table 1 below. The analytical results obtained are shown in Table 2.

In Examples 7, 8, 14, and 15, the optically active alcohol produced contains two asymmetric centers forming diastereomers. A ratio of the syn form to the anti form in each case was determined by HPLC, and the optical yield of each form was determined. The results obtained are separately shown in Table 3.

TABLE 1

Substrate

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        O
        ‖
        C     COR2
       / \   /
     R1   CH
          |
          R3
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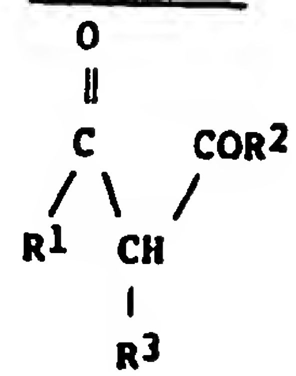
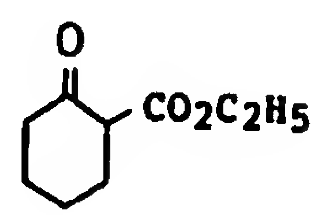
Example No.	R^1	R^2	R^3	Catalyst	Substrate/ Catalyst (mol/mol)	Hydrogen Pressure (kg/cm^2)	Tempera- Ture (°C)	Time (hr)
2	CH_3	OC_2H_5	H	$Ru_2Cl_4[(+)\text{-BINAP}]_2(NEt_3)$	2000	40	30	22
3	CH_3	OiPr	H	$[Ru((-)\text{-BINAP})](ClO_4)_2$	1000	5	30	20
4	CH_3	OtBu	H	$[Ru((-)\text{-T-BINAP})](BF_4)_2$	1000	5	30	20
5	CH_3CH_2	OCH_3	H	$Ru_2Cl_4[(+)\text{-BINAP}]_2(NEt_3)$	2000	40	30	18
6	$CH_3(CH_2)_3$	OCH_3	H	$Ru_2Cl_4[(+)\text{-T-BINAP}]_2(NEt_3)$	1000	40	30	18
7	CH_3	OC_2H_5	Cl	$[RuH((+)\text{-BINAP})_2]ClO_4$	1000	30	30	15
8	CH_3	OC_2H_5	CH_3	$Ru_2Cl_4[(-)\text{-T-BINAP}]_2(NEt_3)$	1000	80	30	24
9	CF_3	OC_2H_5	H	$RuHCl[(+)\text{-BINAP}]_2$	1000	80	30	16
10	$PhCH_2OCH_2$	OCH_3	H	$Ru_2Cl_4[(-)\text{-T-BINAP}]_2(NEt_3)$	1000	40	30	20
11	CH_3	$NHCH_2Ph$	H	$[Ru((-)\text{-T-BINAP})](PF_6)_2$	1000	40	30	20
12	$(CH_3)_2NCH_2$	OC_2H_5	H	$Ru_2Cl_4[(+)\text{-BINAP}]_2(NEt_3)$	1000	40	30	18
13	CH_3	SC_2H_5	H	$[Ru((+)\text{-T-BINAP})](ClO_4)_2$	1000	40	30	30

TABLE 1 (cont'd)

Substrate



Example No.	R^1	R^2	R^3	Catalyst	Substrate/ Catalyst (mol/mol)	Hydrogen Pressure (kg/cm^2)	Tempera- Ture (°C)	Time (hr)
14				$[Ru((+)\text{-}BINAP)](BF_4)_2$	1000	40	30	24
15	CH_3	OCH_3	$CH_2CO_2CH_3$	$RuHCl[(-)\text{-}T\text{-}BINAP]_2$	1000	40	30	36
16	$ClCH_2$	CH_3	H	$Ru_2Cl_4[(+)\text{-}BINAP]_2(NEt_3)$	1000	100	30	16
17	$BrCH_2$	CH_3	H	$Ru_2Cl_4[(-)\text{-}BINAP]_2(NEt_3)$	1000	40	30	20

Note: iPr represents an isopropyl group; tBu represents a t-butyl group; and Ph represents a phenyl group.

TABLE 2

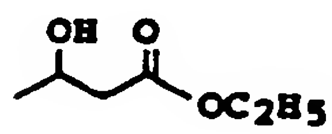
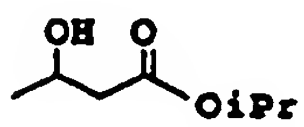
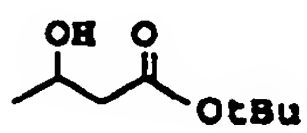
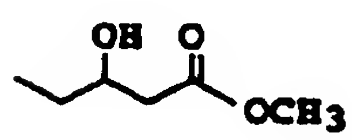
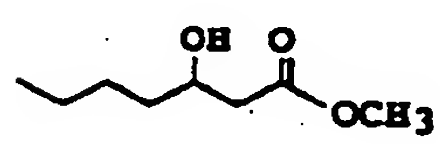
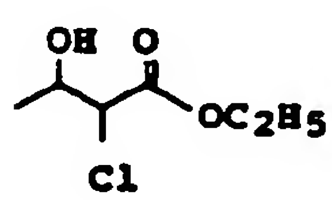
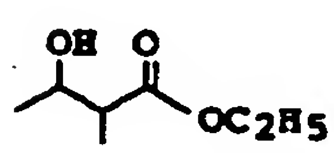
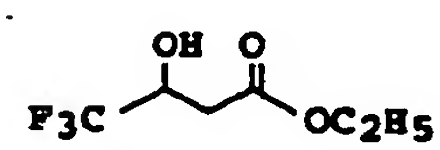
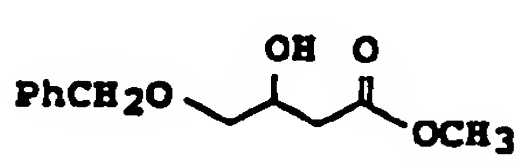
Example No.	Product	Yield (%)	Optical Yield (%ee)
2		99	99.1
3		98	98.0
4		98	96.4
5		99	99.3
6		99	99.2
7		95	see Table 3
8		97	see Table 3
9		95	46
10		97	95

TABLE 2 (cont'd)

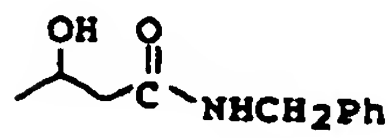
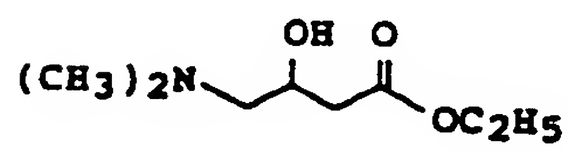
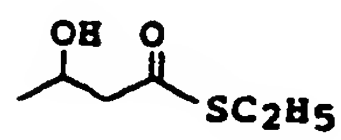
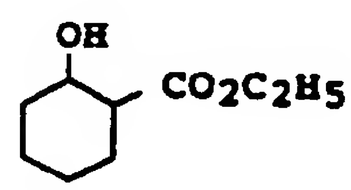
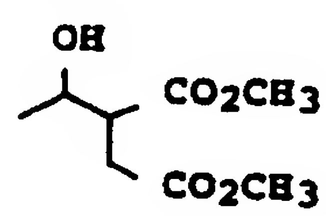
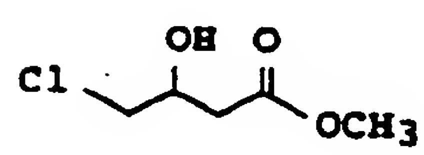
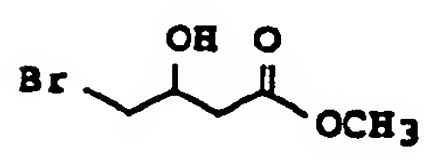
Example No.	Product	Yield (%)	Optical Yield (%ee)
11		94	88
12		91	93
13		87	65
14		90	see Table 3
15		85	see Table 3
16		90	67
17		95	45

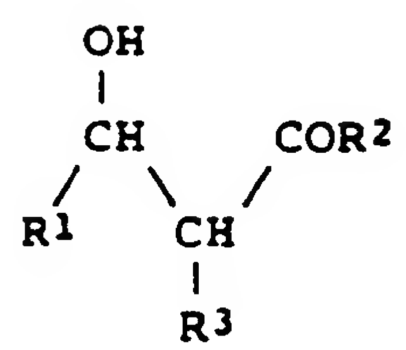
TABLE 3

Example No.	Syn:Anti Ratio	Optical Yield (%ee)	
		Syn	Anti
7	60:40	92	88
8	50:50	90	87
14	55:45	91	89
15	60:40	92	86

As described above, the present invention provides an industrially valuable process for preparing a useful optically active alcohol at high efficiency.

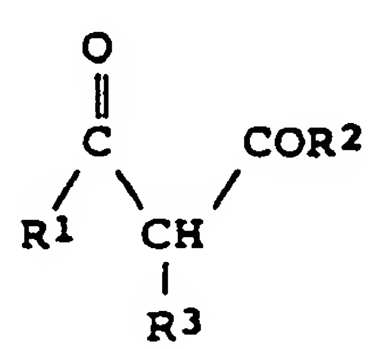
Claims

1. A process for preparing an optically active alcohol represented by formula (I):



(I)

wherein R^1 represents a substituted or unsubstituted alkyl group having 1 to 7 carbon atoms, a trifluoromethyl group or an aryl group; R^2 represents OR^4, wherein R^4 represents an alkyl group having from 1 to 8 carbon atoms, SR^5, wherein R^5 represents an alkyl group having 1 to 7 carbon atoms or a phenyl group, or NR^6R^7, wherein R^6 and R^7, which may be the same or different, each represents a hydrogen atom, an alkyl group having 1 to 7 carbon atoms or a benzyl group; and R^3 represents a hydrogen atom, a halogen atom, an alkyl group having 1 to 7 carbon atoms, a C1-8 alkoxycarbonyl group or a C1-8 alkoxycarbonyl-C1-7 alkyl group; or R^1 and R^3 are connected to each other to form a methylene chain, forming a 4- to 6-membered ring together with the carbon atoms therebetween,
which comprises asymmetrically hydrogenating a β-keto acid derivative represented by formula (II):



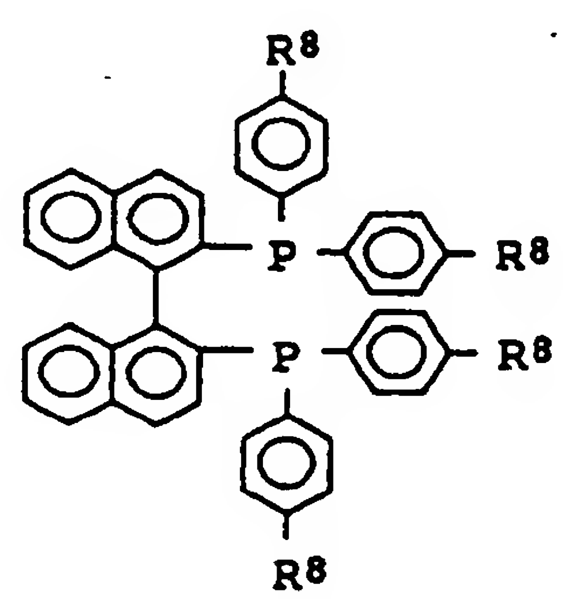
(II)

wherein R^1, R^2, and R^3 are as defined above,
in the presence of a ruthenium-optically active phosphine complex as a catalyst.

2. A process as claimed in Claim 1, wherein said ruthenium-optically active phosphine complex is a compound represented by formula (III):

$$Ru_xH_yCl_z(R^8\text{-BINAP})_2(S)_p \qquad (III)$$

wherein R^8-BINAP represents a tertiary phosphine represented by formula (IV):



(IV)

wherein R^8 represents a hydrogen atom, a methyl group or a t-butyl group; S represents a tertiary amine; when y represents 0, then x represents 2, z represents 4, and p represents 1; and when y represents 1, then x represents 1, z represents 1, and p represents 0,
or a compound represented by formula (V):

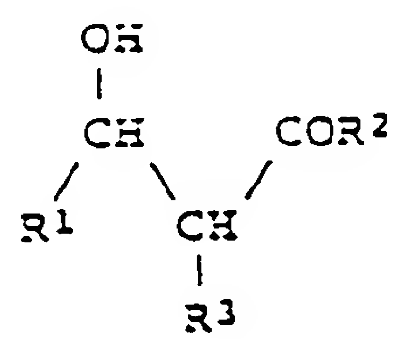
$$[RuH_\ell(R^8\text{-BINAP})_v]Y_w \qquad (V)$$

wherein R^8-BINAP is as defined above; Y represents ClO_4, BF_4 or PF_6; when ℓ represents 0, then v represents 1, and w represents 2; and when ℓ represents 1, then v represents 2 and w represents 1.

3. A process as claimed in Claim 1 or 2, wherein the derivative formulae (II) is dissolved in an amphiprotic solvent and the phosphine complex is added in an amount of 1/100 to 1/50,000 mol per mol of the derivative (I).

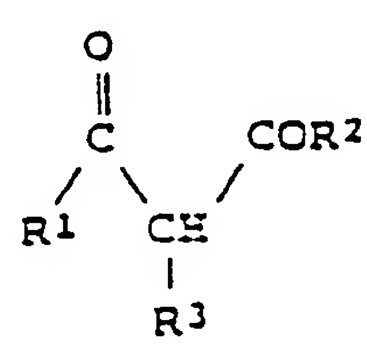
Patentansprüche

1. Verfahren zur Herstellung eines optisch aktiven Alkohols der Formel (I):



(I)

worin R^1 eine substituierte oder unsubstituierte Alkylgruppe mit 1 bis 7 Kohlenstoffatomen, eine Trifluormethylgruppe oder eine Arylgruppe darstellt; R^2 OR^4 ist, worin R^4 eine Alkylgruppe mit 1 bis 8 Kohlenstoffatomen ist, SR^5, worin R^5 eine Alklygruppe mit 1 bis 7 Kohlenstoffatomen oder eine Phenylgruppe ist, oder NR^6R^7 ist, worin R^6 und R^7, die gleich oder verschieden sein können, je ein Wasserstoffatom, eine Alkylgruppe mit 1 bis 7 Kohlenstoffatomen oder eine Benzylgruppe darstellen, und R^3 ein Wasserstoffatom, ein Halogenatom, eine Alkylgruppe mit 1 bis 7 Kohlenstoffatomen, eine C1-8 Alkoxycarbonylgruppe oder eine C1-8 Alkoxycarbonyl-C1-7 Alkylgruppe bedeutet oder R^1 und R^3 miteinander unter Bildung einer Methylenkette verbunden sind, wobei mit den dazwischenliegenden Kohlenstoffatomen ein 4-6 gliedriger Ring gebildet wird,
welches Verfahren die asymmetrische Hydrierung eines β-keto-Säurederivates der Formel (II):



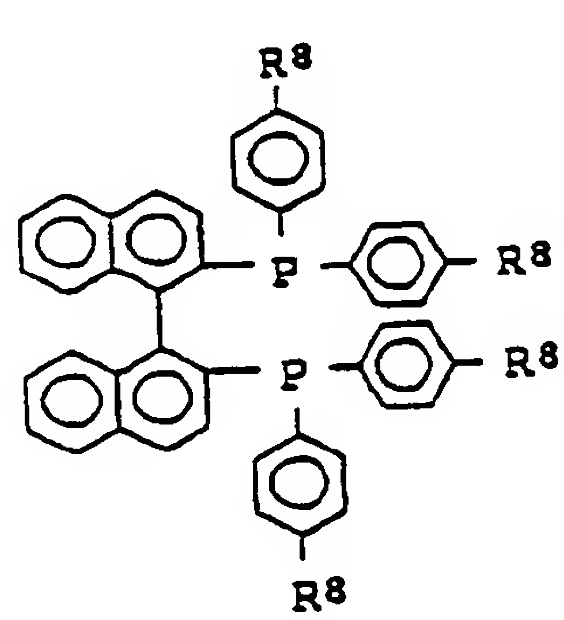
(II)

worin R^1, R^2 und R^3 wie oben definiert sind, in Gegenwart eines Komplexes von Ruthenium mit optisch aktivem Phosphin als Katalysator umfasst.

2. Verfahren gemäss Anspruch 1, worin der genannte Komplex von Ruthenium mit optisch aktivem Phosphin eine Verbindung der Formel (III) ist:

$$Ru_xH_yCl_z(R^8\text{-BINAP})_2(S)_p \qquad \text{(III)}$$

worin R^8-BINAP ein tertiäres Phosphin der Formel (IV):



(IV)

darstellt, worin R^8 ein Wasserstoffatom, eine Methylgruppe oder eine t-Butylgruppe bedeutet; S ein tertiäres Amin bedeutet; wenn y 0 ist, x 2, z 4 und p 1 bedeutet; und wenn y 1 ist, bedeutet x 1, z 1 und p 0 bedeutet, oder eine Verbindung der Formel (V):

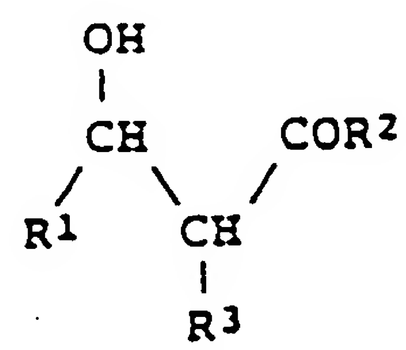
$$[RuH_l(R^8\text{-BINAP})_v]Y_w \qquad (V)$$

darstellt, worin R^8-BINAP wie oben definiert ist; Y ClO_4, BF_4 oder PF_6; darstellt; wenn l 0 ist, v 1 und w 2 bedeutet; und wenn l 1 ist, v 2 und w 1 bedeutet.

3. Verfahren gemäss Anspruch 1 oder 2, worin das Derivat der Formel (II) in einem amphiprotischen Lösungsmittel aufgelöst wird und der Phosphinkomplex in einer Menge von 1/100 bis 50 000 mol pro mol Derivat (I) zugefügt wird.

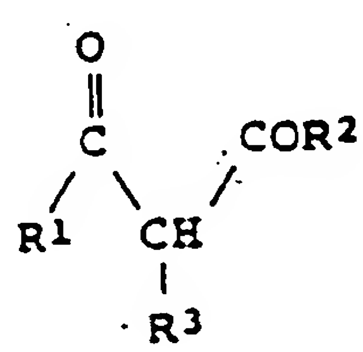
Revendications

1. Procédé de préparation d'un alcool optiquement actif représenté par la formule (I):



(I)

où R^1 représente un groupe alkyle substitué ou non-substitué ayant 1 à 7 atomes de carbone, un groupe trifluorométhyle ou un groupe aryle; R^2 représente OR^4 dans lequel R^4 représente un groupe alkyle ayant 1 à 8 atomes de carbone, SR^5 dans lequel R^5 représente un groupe alkyle ayant 1 à 7 atomes de carbone ou un groupe phényle, ou NR^6R^7 dans lequel R^6 et R^7, qui peuvent être pareils ou différents, représentent chacun un atome d'hydrogène, un groupe alkyle ayant 1 à 7 atomes de carbone ou un groupe benzyle; et R^3 représente un atome d'hydrogène, un atome d'halogène, un groupe alkyle ayant 1 à 7 atomes de carbone, un groupe alkoxy en C1-8-carbonyle ou un groupe alkoxy en C1-8-carbonyle-alkyle en C1-7; ou R^1 et R^3 sont connectés l'un à l'autre pour former une chaîne méthylène formant ensemble avec les atomes de carbone situés entre eux, un anneau de 4 à 6 membres,
procédé comprenant l'hydrogénation asymétrique d'un dérivé de β-céto-acide représenté par la formule (II):



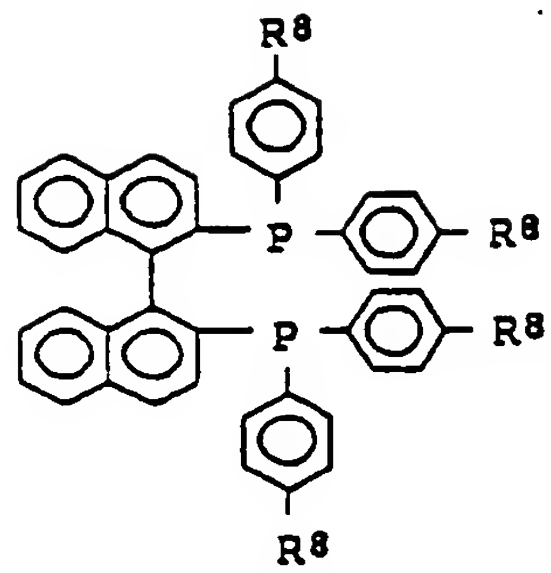
(II)

où R^1, R^2 et R^3 sont tels que définis plus haut en présence d'un complexe de ruthénium-phosphine optivement active comme catalyseur.

2. Procédé selon la revendication 1, où le dit complexe de ruthénium-phosphine optiquement active est un composé représenté par la formule (III):

$$Ru_xH_yCl_z(R^8\text{-BINAP})_2(S)_p \qquad (III)$$

où R^8-BINAP représente une phosphine tertiaire représentée par la formule (IV):



(IV)

où R^8 représente un atome d'hydrogène, un groupe méthyle ou un groupe t-butyle; S représente une amine tertiaire; lorsque y représente 0, x représente alors 2, z représente 4 et p représente 1; et lorsque y représente 1, x représente alors 1, z représente 1 et p représente 0, ou un composé représenté par la formule (V) :

$$[RuH_{\ell}(R^8\text{-}BINAP)_v]Y_w \qquad (III)$$

où R^8-BINAP est tel que défini ci-dessus; Y représente ClO_4 BF_4 ou PF_6; lorsque ℓ représente 0, v représente alors 1 et w représente 2; et lorsque ℓ représente 1, v représente alors 2 et w représente 1.

3. Procédé selon la revendication 1 ou la revendication 2, dans lequel on dissout le dérivé de la formule (II) dans un solvant amphotère et on ajoute le complexe de phosphine dans une quantité de 1/100 à 1/50000 mole par mole du dérivé (I).